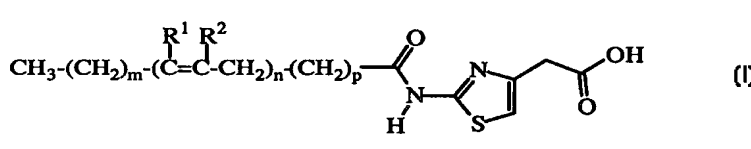




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(54) Title: (2-ACYLAMINOTHIAZOLE-4-YL)ACETIC ACID DERIVATIVES <div style="text-align: center;">  <p style="text-align: right;">(I)</p> </div> (57) Abstract <p>This invention provides compounds of Formula (I) having structure (I), wherein R¹, R² are both hydrogen or form a bond, or are each, independently, alkyl of 1-6 carbon atoms or aryl of 6-12 carbon atoms; m = 0-10; n = 1-3; and p = 0-10; with the proviso that m + p is less than or equal to 15; or a pharmaceutically acceptable salt thereof, which are useful in treating metabolic disorders related to insulin resistance or hyperglycemia.</p>		

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(2-ACYLAMINOTHIAZOLE-4-YL)ACETIC ACID DERIVATIVES**BACKGROUND OF THE INVENTION**

5 The prevalence of insulin resistance in glucose intolerant subjects has long been recognized. Reaven et al (*American Journal of Medicine* 1976, 60, 80) used a continuous infusion of glucose and insulin (insulin/glucose clamp technique) and oral glucose tolerance tests to demonstrate that insulin resistance existed in a diverse group of nonobese, nonketotic subjects. These subjects ranged from borderline glucose
10 tolerant to overt, fasting hyperglycemia. The diabetic groups in these studies included both insulin dependent (IDDM) and noninsulin dependent (NIDDM) subjects.

Coincident with sustained insulin resistance is the more easily determined hyperinsulinemia, which can be measured by accurate determination of circulating plasma insulin concentration in the plasma of subjects. Hyperinsulinemia can be
15 present as a result of insulin resistance, such as is in obese and/or diabetic (NIDDM) subjects and/or glucose intolerant subjects, or in IDDM subjects, as a consequence of over injection of insulin compared with normal physiological release of the hormone by the endocrine pancreas.

The association of hyperinsulinemia with obesity and with ischemic diseases of
20 the large blood vessels (e.g. atherosclerosis) has been well established by numerous experimental, clinical and epidemiological studies (summarized by Stout, *Metabolism* 1985, 34, 7, and in more detail by Pyorala et al, *Diabetes/Metabolism Reviews* 1987, 3, 463). Statistically significant plasma insulin elevations at 1 and 2 hours after oral glucose load correlates with an increased risk of coronary heart disease.

25 Since most of these studies actually excluded diabetic subjects, data relating the risk of atherosclerotic diseases to the diabetic condition are not as numerous, but point in the same direction as for nondiabetic subjects (Pyorala et al). However, the incidence of atherosclerotic diseases in morbidity and mortality statistics in the diabetic population exceeds that of the nondiabetic population (Pyorala et al; Jarrett *Diabetes/Metabolism*
30 *Reviews* 1989,5, 547; Harris et al, Mortality from diabetes, in *Diabetes in America* 1985).

The independent risk factors obesity and hypertension for atherosclerotic diseases are also associated with insulin resistance. Using a combination of insulin/glucose clamps, tracer glucose infusion and indirect calorimetry, it has been
35 demonstrated that the insulin resistance of essential hypertension is located in peripheral tissues (principally muscle) and correlates directly with the severity of hypertension

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(DeFronzo and Ferrannini, *Diabetes Care* 1991, 14, 173). In hypertension of the obese, insulin resistance generates hyperinsulinemia, which is recruited as a mechanism to limit further weight gain via thermogenesis, but insulin also increases renal sodium reabsorption and stimulates the sympathetic nervous system in kidneys, heart, and vasculature, creating hypertension.

It is now appreciated that insulin resistance is usually the result of a defect in the insulin receptor signaling system, at a site post binding of insulin to the receptor. Accumulated scientific evidence demonstrating insulin resistance in the major tissues which respond to insulin (muscle, liver, adipose), strongly suggests that a defect in insulin signal transduction resides at an early step in this cascade, specifically at the insulin receptor kinase activity, which appears to be diminished (reviewed by Haring, *Diabetologia* 1991, 34, 848).

Protein-tyrosine phosphatases (PTPases) play an important role in the regulation of phosphorylation of proteins. The interaction of insulin with its receptor leads to phosphorylation of certain tyrosine molecules within the receptor protein, thus activating the receptor kinase. PTPases dephosphorylate the activated insulin receptor, attenuating the tyrosine kinase activity. PTPases can also modulate post-receptor signaling by catalyzing the dephosphorylation of cellular substrates of the insulin receptor kinase. The enzymes that appear most likely to closely associate with the insulin receptor and therefore, most likely to regulate the insulin receptor kinase activity, include PTP1B, LAR, PTP α and SH-PTP2 (B. J. Goldstein, *J. Cellular Biochemistry* 1992, 48, 33; B. J. Goldstein, *Receptor* 1993, 3, 1-15.; F. Ahmad and B. J. Goldstein *Biophys Acta* 1995, 1248, 57-69).

McGuire et al. (*Diabetes* 1991, 40, 939), demonstrated that nondiabetic glucose intolerant subjects possessed significantly elevated levels of PTPase activity in muscle tissue vs. normal subjects, and that insulin infusion failed to suppress PTPase activity as it did in insulin sensitive subjects.

Meyerovitch et al (*J. Clinical Invest.* 1989, 84, 976) observed significantly increased PTPase activity in the livers of two rodent models of IDDM, the genetically diabetic BB rat, and the STZ-induced diabetic rat. Sredy et al (*Metabolism*, 44, 1074, 1995) observed similar increased PTPase activity in the livers of obese, diabetic ob/ob mice, a genetic rodent model of NIDDM.

The compounds of this invention have been shown to inhibit rat-derived and human-derived recombinant PTPase-1B (rPTP-1B) *in vitro*. They are useful in the

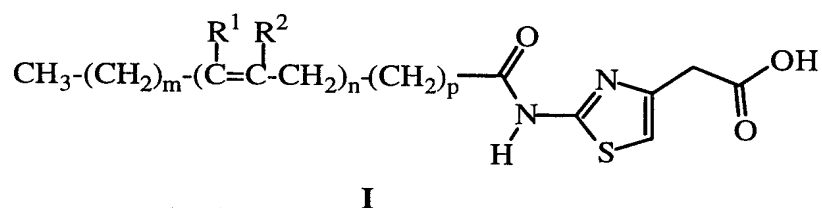
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treatment of insulin resistance associated with obesity, glucose intolerance, diabetes mellitus, hypertension and ischemic diseases of the large and small blood vessels.

2-Aminothiazoleacetic acid derivatives have been used extensively in chemical and patent literature as intermediates for penam and cepham classes of antibiotics, but the long (C₁₆, C₁₈) unsaturated carboxamide chains at C₂ of the thiazoleacetic acid moiety makes these compounds novel. WO 9616650 and JP 07149745 generically claim "lower alkyl" amides of 2-aminothiazoleacetic acid are antibacterial and antiinflammatory (elastase inhibitors) agents, respectively. U.S. patent 5,688,821 (1997, to AHP) teaches that some of the same compounds that are in this invention are inhibitors of the enzymes phospholipase A₂ derived from human sources (anti-inflammatory agents), but others are not and vice-versa. Certain long acylhydrocarbon chain derivatives of 2-aminothiazoleacetic acid have been prepared (Toth, *Liebigs Ann. Chem.* EN, 7, 685, 1994).

15 DESCRIPTION OF THE INVENTION

This invention provides a method of using a compound of formula I having the structure



20 wherein

R¹, R² are both hydrogen or form a bond, or are each, independently, alkyl of 1-6 carbon atoms or aryl of 6-12 carbon atoms;

m = 0 - 10;

n = 1-3; and

25 p = 0 - 10;

with the proviso that m + p is less than or equal to 15;

or a pharmaceutically acceptable salt thereof in the treatment of metabolic disorders related to insulin resistance or hyperglycemia, primary hypertension, or atherosclerosis.

30 Pharmaceutically acceptable salts can be formed from organic and inorganic bases, such as alkali metals (sodium, potassium, or lithium), alkaline earth metals (calcium or magnesium), ammonium, primary, secondary alkyl amines, or tertiary alkyl

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amines. The use of tromethamine salts of the compounds of this invention showed improved water solubility and bioavailability.

5 It is understood that the compounds of this invention can exhibit E (trans) or Z (cis) stereoisomerism about the double bond, and that this invention covers both the E and Z isomers, at each double bond, and in particular when R¹ and R² are both hydrogen, alkyl, or aryl. When R¹ and R² are not a bond, it is preferred that they both are hydrogen.

10 Preferred compounds of this invention are those in which:

m = 1 and n = 3 and p = 6;

m = 4 and n = 3 and p = 3;

m = 5 and n = 1 and p = 6 or 8;

m = 7 and n = 1 and p = 6; and

15 m = 10 and n = 1 and p = 3.

Aryl is defined as an organic radical derived from an aromatic hydrocarbon by the removal of a hydrogen (i.e., phenyl from benzene). It is preferred that the aryl moiety is a phenyl or naphthyl group; with phenyl being most preferred. The aryl
20 moiety may be optionally mono-, di-, or tri- substituted with a substituent selected from the group consisting of alkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, trifluoromethyl, halogen, alkoxycarbonyl of 2-7 carbon atoms, alkylamino of 1-6 carbon atoms, and dialkylamino in which each of the alkyl groups is of 1-6 carbon atoms, nitro, cyano, -CO₂H, alkylcarbonyloxy of 2-7 carbon atoms, and alkylcarbonyl
25 of 2-7 carbon atoms.

The compounds of this invention can be synthesized by saponification of the corresponding 2-fatty acylaminothiazole-4-acetic acid ethyl esters, followed by acidification of the reaction mixture. Basic salts of these acids are prepared also in a conventional manner as is known in the art. In particular the tromethamine salts of this
30 invention provide water soluble derivatives for improved bioavailability. The fatty acylaminothiazoleacetic acid esters are prepared in one of two ways: condensation of ethyl-2-aminothiazoleacetate with a fatty acid chloride in the presence of a tertiary amine base such as triethylamine or diisopropylethylamine in an aprotic solvent (e.g. dichloromethane or tetrahydrofuran) at ice temperature (Procedure A) or, preferably,
35 directly from the fatty acid with the aid of an organodiimide coupling agent as is well

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known in the synthesis of peptides (Procedure B). The fatty acyl starting materials are either prepared according to standard chemical methodology (such as Wittig or Peterson olefination reactions and or modifications thereof, or by reductive dicarbonyl coupling reactions, such as those procedures of McMurry, Corey and Mukiyama), or from
5 commercially available starting materials. General procedures to prepare representative compounds of this invention are disclosed in U.S. Patent 5,688,821, which is hereby incorporated by reference, and the preparation of specific representative compounds of this invention are provided in Examples which follow.

10 The compounds of this invention are useful in treating metabolic disorders related to insulin resistance or hyperglycemia, typically associated with obesity or glucose intolerance. The compounds of this invention are therefore, particularly useful in the treatment or inhibition of type II diabetes. The compounds of this invention are also useful in modulating glucose levels in disorders such as type I diabetes.
15 Additionally, because an association exists between insulin resistance and hypertension and between insulin resistance, hypertension and coronary artery disease, the compounds of this invention are also useful for the treatment of primary (essential) hypertension and atherosclerosis.

20 The ability of compounds of this invention to treat or inhibit disorders related to insulin resistance or hyperglycemia was established with representative compounds of this invention in the following pharmacological test procedures which measure the inhibition of PTPase.

25 Inhibition of recombinant rat protein tyrosine phosphatase 1B (rPTP1B) activity using p-nitrophenylphosphate as a substrate.

Measurement of pNPPase activity. The assay is conducted as described by Moss (Acid Phosphatases. In: Methods of Enzymatic Analysis, Enzymes 2: Esterases, Glycosidases, Lyases, Ligases. Bergmeyer, H.U., ed. Weinheim: Verlag Chemie
30 GmBH, 1984: 92) and Tonks, et al., *J. Biol. Chem.* **263**, 6731, **1988**), with minor modifications. The incubation mixture contains in a final volume of 0.24 ml: 50 mM HEPES (pH 7.4), 6.33 mM p-nitrophenyl phosphate and 5/25/100 µM compound suspended in 1.25% DMSO. rPTP1B (obtained from the laboratory of Dr. Barry
35 Goldstein of Thomas Jefferson University. The enzyme (see Goldstein et al. *Mol. Cell. Biochem.* **109**, 107, **1992**), in microvials containing 500-700 µg/ml protein in

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33 mM TRIS-HCl, 2 mM EDTA, 10% glycerol and 10 mM 2-mercaptoethanol) is preincubated with drug in HEPES buffer for ten minutes at 37°C. The reaction is started by the addition of p-nitrophenyl phosphate and after 30 minutes at 37°C, the reaction is terminated by adding 1 ml of 0.1 N NaOH. The assay is performed in triplicate and the reaction mixture contains approximately 3.3 µg/ml protein, the above components, plus: 5.50 mM TRIS-HCl, 8.33 mM 2-mercaptoethanol, 0.33 mM EDTA and 1.67% glycerol. The samples are read at 410 nm in a spectrophotometer and are evaluated based on a calibration curve of p-nitrophenol standard solution.

Compounds were screened robotically at a single concentration of ~25 µM. The results are expressed as percent of control, in that the amount of p-nitrophenol formed in the compound treated samples (nmol/minute/mg protein) is compared to the amount (nmol/minute/mg protein) formed in the untreated samples. p-Nitrophenylphosphatase activity is also determined in each experiment and is expressed per minute per mg protein. Representative results are given in Table 1.

Inhibition of recombinant human protein tytosine phosphatase 1B

A representative compound (Example 8) of this invention was also evaluated for inhibition of recombinant human PTP1B.

Human recombinant PTP1B was prepared as described by Goldstein (see Goldstein et al. *Mol. Cell. Biochem.* **109**, 107, 1992). The enzyme preparation used was in microtubes containing 500-700 µg/ml protein in 33 mM Tris-HCl, 2 mM EDTA, 10% glycerol and 10 mM 2-mercaptoethanol.

Measurement of PTPase activity. The malachite green-ammonium molybdate method, as described (Lanzetta et al. *Anal. Biochem.* **100**, 95, 1979) and adapted for a platereader, is used for the nanomolar detection of liberated phosphate by recombinant PTP1B. The assay uses, as substrate, a dodecaphosphopeptide custom synthesized by AnaSpec, Inc. (San Jose, CA). the peptide, TRDIYETDYRK, corresponding to the 1142-1153 catalytic domain of the insulin receptor, is tyrosine phosphorylated on the 1146, 1150, and 1151 tyrosine residues. The recombinant rPTP1B is diluted with buffer (pH 7.4, containing 33 mM Tris-HCl, 2 mM EDTA and 50 mM b-mercaptoethanol) to obtain an approximate activity of 1000-2000 nmoles/min/mg protein. The diluted enzyme (83.25 mL) is preincubated for 10 min at 37°C with or without test compound (6.25 mL) and 305.5 mL of the 81.83 mM HEPES reaction buffer, pH 7.4 peptide substrate, 10.5 ml at a final concentration of 50 mM, and is equilibrated to 37°C. in a LABLINE Multi-Blok heater equipped with a

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titerplate adapter. The preincubated recombinant enzyme preparation (39.5 ml) with or without drug is added to initiate the dephosphorylation reaction, which proceeds at 37°C for 30 min. The reaction is terminated by the addition of 200 mL of the malachite green-ammonium molybdate-Tween 20 stopping reagent (MG/AM/Tw). The stopping reagent consists of 3 parts 0.45% malachite green hydrochloride, 1 part 4.2% ammonium molybdate tetrahydrate in 4 N HCl and 0.5% Tween 20. Sample blanks are prepared by the addition of 200 mL MG/AM/Tw to substrate and followed by 39.5 ml of the preincubated recombinant enzyme with or without drug. The color is allowed to develop at room temperature for 30 min. and the sample absorbances are determined at 650 nm using a platereader (Molecular Devices). Sample and blanks are prepared in quadruplicates.

PTPase activities, based on a potassium phosphate standard curve, are expressed as nmoles of phosphate released/min/mg protein. Inhibition of recombinant PTP1B by test compounds is calculated as percent of phosphatase control. A four parameter non-linear logistic regression of PTPase activities using SAS release 6.08, PROC NLIN, is used for determining IC₅₀ values of test compounds. Representative results are given in Table 2 .

TABLE 1. Inhibition of recombinant phosphotyrosine phosphatase 1B by compounds of this invention.

Example	% inhibition ^a
1	93.4
2	93.9
3	58.16
4	84.8
5	94.97
6	93.77
7	83.8
8	96.6
9	92.4
(NH ₄)Mo ₇ O ₂₄ • 4 H ₂ O	92.3
Na ₃ VO ₄	86.3

^a All compounds administered at 25 µM

TABLE 2. Dose-response inhibition data and IC₅₀ for Example 8 vs rPTP1B (human)

% inhibition	Dose (μM)
100	10
96.8	2.5
94.94	1
73.21	0.5
43.25	0.25
25.53	0.1
IC₅₀:	0.267

5 Based on the results obtained in the standard pharmacological test procedures, representative compounds of this invention have been shown to inhibit PTPase activity, and are therefore useful in treating metabolic disorders related to insulin resistance or hyperglycemia, typically associated with obesity or glucose intolerance. More particularly, the compounds of this invention are useful in the treatment or inhibition of
10 type II diabetes, and in modulating glucose levels in disorders such as type I diabetes. The compounds of this invention are also useful in the treatment of primary (essential) hypertension and atherosclerosis. As used herein, the term modulating means maintaining glucose levels within clinically normal ranges.

15 Effective administration of these compounds may be given at a daily dosage of from about 1 mg/kg to about 250 mg/kg, and may given in a single dose or in two or more divided doses. Such doses may be administered in any manner useful in directing the active compounds herein to the recipient's bloodstream, including orally, via implants, parenterally (including intravenous, intraperitoneal and subcutaneous
20 injections), rectally, vaginally, and transdermally. For the purposes of this disclosure, transdermal administrations are understood to include all administrations across the surface of the body and the inner linings of bodily passages including epithelial and mucosal tissues. Such administrations may be carried out using the present compounds, or pharmaceutically acceptable salts thereof, in lotions, creams, foams,
25 patches, suspensions, solutions, and suppositories (rectal and vaginal).

Compounds of this invention may be administered neat or with a pharmaceutical carrier to a patient in need thereof. The pharmaceutical carrier may be solid or liquid.

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Oral formulations containing the active compounds of this invention may comprise any conventionally used oral forms, including tablets, capsules, buccal forms, troches, lozenges and oral liquids, suspensions or solutions. Capsules may contain mixtures of the active compound(s) with inert fillers and/or diluents such as the pharmaceutically acceptable starches (e.g. corn, potato or tapioca starch), sugars, artificial sweetening agents, powdered celluloses, such as crystalline and microcrystalline celluloses, flours, gelatins, gums, etc. Useful tablet formulations may be made by conventional compression, wet granulation or dry granulation methods and utilize pharmaceutically acceptable diluents, binding agents, lubricants, disintegrants, suspending or stabilizing agents, including, but not limited to, magnesium stearate, stearic acid, talc, sodium lauryl sulfate, microcrystalline cellulose, carboxymethyl-cellulose calcium, polyvinylpyrrolidone, gelatin, alginic acid, acacia gum, xanthan gum, sodium citrate, complex silicates, calcium carbonate, glycine, dextrin, sucrose, sorbitol, dicalcium phosphate, calcium sulfate, lactose, kaolin, mannitol, sodium chloride, talc, dry starches and powdered sugar. Oral formulations herein may utilize standard delay or time release formulations to alter the absorption of the active compound(s). Suppository formulations may be made from traditional materials, including cocoa butter, with or without the addition of waxes to alter the suppository's melting point, and glycerin. Water soluble suppository bases, such as polyethylene glycols of various molecular weights, may also be used.

It is understood that the dosage, regimen and mode of administration of these compounds will vary according to the malady and the individual being treated and will be subject to the judgment of the medical practitioner involved. It is preferred that the administration of one or more of the compounds herein begin at a low dose and be increased until the desired effects are achieved.

The following procedures describe the preparation of representative examples of this invention.

30

Example 1 (Procedure A): 2-[(*Z*)-1-Oxo-9-octadecenyl]amino]-4-thiazole-acetic acid

A mixture of ethyl 2-aminothiazoleacetic acid (4.6 g, 24.7 mmol) and triethylamine (4.2 mL, 20.3 mmol) in dichloromethane (125 mL) was cooled in an ice bath under N₂ atmosphere. Oleoyl chloride (neat 75%, 11 mL, 25 mmol) was added

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dropwise and the reaction was then allowed to warm to room temperature. After 15 h at room temperature 10% aqueous HCl solution was added to the reaction mixture, stirred for 2 h and then poured onto saturated aqueous brine solution in a separatory funnel. The organic layer was separated, dried over anhydrous MgSO₄, filtered and concentrated on a rotary evaporator to a yellow oil. The crude ester was purified by HPLC (70% hexane, 30% EtOAc) to give 4 g of ethyl-2-[(Z)-1-oxo-9-octadecenyl]amino]-4-thiazoleacetate, as a yellow oil. IR (film) μ (cm⁻¹): 1745, 1700. MS (EI) m/z 450 (M⁺).

Ethyl-2-[(Z)-1-oxo-9-octadecenyl]amino]-4-thiazoleacetate (4 g, 8.89 mmol), sodium hydroxide (0.79 g, 19.8 mmol) and tetrahydrofuran (50 mL) were combined and cooled in an ice bath under N₂ atmosphere. Enough distilled water was added to the mixture to dissolve the hydroxide and provide a homogeneous solution. The reaction was kept at 0°C for 2 h, then allowed to warm to room temperature and stirred overnight. Aqueous 10% HCl solution was added to the mixture, and stirring continued for 1 h. Ethyl acetate and saturated aqueous brine solution were added to the mixture, and the organic phase was separated and dried over MgSO₄. After filtration and concentration the crude dark amber oil was treated with ether, stirred for 0.5 h and the product was collected on a Buchner funnel and air dried to give 1.5 g of the title compound as a white solid, mp 106-108.5 °C.

Analysis for: C₂₃H₃₈N₂O₃S

Calc'd: C, 65.36; H, 9.06; N, 6.63

Found: C, 64.99; H, 9.19; N, 6.57

Example 2 (Procedure B): 2-[(E)-1-Oxo-9-octadecenyl]amino]-4-thiazole-acetic acid

A mixture of elaidic acid (5.1 g, 17.7 mmol; 98%), ethyl-2-aminothiazoleacetate (3.3 g, 17.7 mmol), triethylamine (2.8 g, 27.7 mmol), 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (5.3 g, 26.9 mmol) and 4-dimethylaminopyridine (0.4 g, 3.3 mmol) was combined in dichloromethane (225 mL) at ice temperature under N₂ atmosphere. The mixture was stirred at 0 °C for 1 h, then allowed to warm to room temperature and stirred for 15 h. The reaction mixture was diluted with water and the organic phase was separated, washed with water and saturated brine solution, dried over MgSO₄, filtered and concentrated to give 7.1 g of ethyl-2-[(E)-1-oxo-9-octadecenyl]-amino]-4-thiazoleacetate, which was used directly without purification.

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A mixture of the above ester (7.4 g, 16.5 mmol) and sodium hydroxide (1.44 g, 36.1 mmol) was combined in THF (150 mL) and cooled in ice under N₂ atmosphere. Enough distilled water was added portionwise until the hydroxide was dissolved (~ 15 mL) and the mixture was maintained at 0 °C for 2 h, then allowed to warm to ambient temperatures with stirring for 15 h. The reaction mixture was evaporated in vacuo, the residue cooled in ice and treated with 2M aqueous HCl solution with stirring. The white precipitate was collected by vacuum filtration, washed with water and air dried. This material was crystallized from boiling heptane, filtered hot, and dried overnight on an abderhalden apparatus (refluxing acetone) to give 4.6 g of the title compound as a white powder, mp 116-118 °C.

Analysis for: C₂₃H₃₈N₂O₃S

Calc'd: C, 65.37; H, 9.06; N, 6.63

Found: C, 65.33; H, 9.15; N, 6.59

Example 3: 2-[(E)-1-Oxo-9-octadecenyl]amino]-4-thiazoleacetic acid, tromethamine (2-amino-2-hydroxymethyl)-1,3-propanediol) salt

A mixture of the title compound of Example 2 (3.0 g 7.1 mmol), tris (hydroxymethyl)amino methane (0.86 g, 7.1 mmol) and absolute ethanol (75 mL) were heated on a hot plate until a homogeneous solution was obtained. The solution was allowed to stand at room temperature for several hours and the solvent removed on a rotary evaporator. The residue was slurried in toluene and the solvent removed in vacuo. The glassy solid was heated under vacuum at 35°C for 24 h to give 3.39 g of the title compound, as a white solid, mp 163-164°C.

Analysis for: C₂₇H₄₉N₃O₆S

Calc'd: C, 59.64; H, 9.08; N, 7.73

Found: C, 59.46; H, 9.05; N, 7.89

Example 4: 2-[(1-Oxo-9-octadecenyl)amino]-4-thiazoleacetic acid

The title compound was prepared by Procedure A (example 1). The crude product was crystallized from hot heptane to give lemon colored crystals, mp 95.5-96.5°C.

Analysis for: C₂₃H₃₆N₂O₃S

Calc'd: C, 65.68; H, 8.63; N, 6.66

Found: C, 65.46; H, 8.53; N, 6.74

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Example 5: 2-(((Z)-1-Oxo-6-octadecynyl)amino)-4-thiazoleacetic acid

The title compound was prepared by the method of procedure B (example 2). The crude product was recrystallized from heptane on a steam bath to provide white
5 crystals, mp 104.5-105.5°C.

Analysis for: C₂₃H₃₈N₂O₃S

Calc'd: C, 65.37; H, 9.06; N, 6.63

Found: C, 65.45; H, 9.06; N, 6.58

10

Example 6: 2-(((Z)-1-Oxo-9-hexadecenyl)amino)-4-thiazoleacetic acid

The title compound was prepared by the method of procedure B. The crude
product was treated with hot heptane (steam bath) cooled to room temperature and
15 collected on a Buchner funnel. The material was air dried for several hours, then in an
Abderhalden apparatus (refluxing acetone) overnight to provide the title compound as a
white waxy solid, mp 108-110°C.

Analysis for: C₂₁H₃₄N₂O₃S

20 Calc'd: C, 63.92; H, 8.68; N, 7.10

Found: C, 64.27; H, 8.86; N, 7.32

Example 7: 2-(((E)-1-Oxo-9-hexadecenyl)amino)-4-thiazoleacetic acid

25 The title compound was prepared by the method of procedure B. The crude
acid was recrystallized from hot heptane to give the product as white crystals, mp 117-
118°C.

Analysis for: C₂₁H₃₄N₂O₃S

30 Calc'd: C, 63.92 ; H, 8.69 ; N, 7.10

Found: C, 63.78 ; H, 8.73 ; N, 6.79

- 13 -

Example 8: 2-(((E)-1-Oxo-11-octadecenyl)amino)-4-thiazoleacetic acid

The title compound was prepared according to the method of procedure B. The crude product was crystallized from hot heptane to give white crystals, mp 115.8-117.1°C.

Analysis for: C₂₃H₃₈N₂O₃S

Calc'd: C, 61.99; H, 9.06; N, 6.63

Found: C, 65.74; H, 8.85; N, 6.32

Example 9: 2-(((Z,Z,Z)-1-Oxo-9,12,15-octadecatrienyl)amino)-4-thiazoleacetic acid

The title compound was prepared by procedure B and precipitated from heptane as a hygroscopic yellow wax.

Analysis for: C₂₃H₃₄N₂O₃S• 1.5 H₂O

Calc'd: C, 61.99; H, 7.92; N, 6.29

Found: C, 62.22; H, 7.68; N, 6.02

Example 10: 2-(((Z,Z,Z)-1-Oxo-6,9,12-octatrienyl)amino)-4-thiazoleacetic acid

The title compound was prepared according to procedure B. The crude product was chromatographed on SiO₂ (flash column, 40 wt. eq., elution with hexane (70%), ethyl acetate (30%), acetic acid (1%)) to give the title compound as a pale yellow wax.

Analysis for: C₂₃H₃₄N₂O₃S

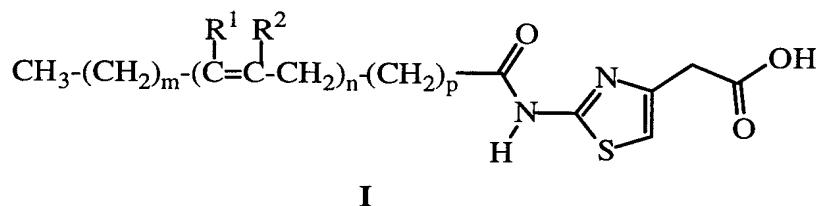
Calc'd: C, 65.99 ; H, 8.91; N, 6.69

Found: C, 65.76 ; H, 8.33; N, 5.50

- 14 -

WHAT IS CLAIMED IS:

1. A method of treating metabolic disorders mediated by insulin resistance or hyperglycemia in a mammal in need thereof which comprises administering to said
 5 mammal, a compound of formula I having the structure



wherein

R^1 , R^2 are both hydrogen or form a bond, or are each, independently, alkyl of 1-6 carbon atoms or aryl of 6-12 carbon atoms;

10 $m = 0 - 10$;

$n = 1-3$; and

$p = 0 - 10$;

with the proviso that $m + p$ is less than or equal to 15;

or a pharmaceutically acceptable salt thereof.

15

2. The method according to claim 1, wherein

$m = 1$ and $n = 3$ and $p = 6$;

$m = 4$ and $n = 3$ and $p = 3$;

$m = 5$ and $n = 1$ and $p = 6$ or 8;

20 $m = 7$ and $n = 1$ and $p = 6$; or

$m = 10$ and $n = 1$ and $p = 3$

or a pharmaceutically acceptable salt thereof.

3. The method according to claim 1, wherein the compound administered is

25 a) 2-[(Z)-1-oxo-9-octadecenyl]amino]-4-thiazoleacetic acid;

b) 2-[(E)-1-oxo-9-octadecenyl]amino]-4-thiazoleacetic acid;

c) 2-[(1-oxo-9-octadecynyl)amino]-4-thiazoleacetic acid;

d) 2-[(Z)-1-oxo-6-octadecenyl]amino]-4-thiazoleacetic acid;

e) 2-[(Z)-1-oxo-9-hexadecenyl]amino]-4-thiazoleacetic acid;

30 f) 2-[(E)-1-oxo-9-hexadecenyl]amino]-4-thiazoleacetic acid;

g) 2-[(E)-1-oxo-11-octadecenyl]amino]-4-thiazoleacetic acid; or

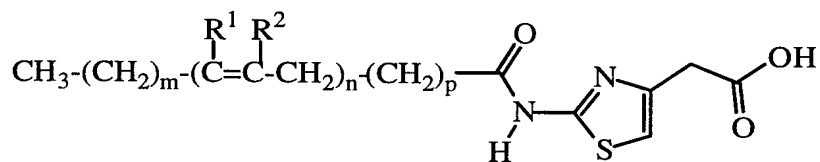
h) 2-[(Z,Z,Z)-1-oxo-9,12,15-octadecatrienyl]amino]-4-thiazoleacetic acid

or a pharmaceutically acceptable salt thereof.

- 15 -

4. A method of treating or inhibiting type II diabetes in a mammal in need thereof which comprises administering to said mammal, a compound of formula I having the structure

5



I

wherein

R^1 , R^2 are both hydrogen or form a bond, or are each, independently, alkyl of 1-6 carbon atoms or aryl of 6-12 carbon atoms;

10 $m = 0 - 10$;

$n = 1-3$; and

$p = 0 - 10$;

with the proviso that $m + p$ is less than or equal to 15;

or a pharmaceutically acceptable salt thereof.

15

5. The method according to claim 4, wherein

$m = 1$ and $n = 3$ and $p = 6$;

$m = 4$ and $n = 3$ and $p = 3$;

$m = 5$ and $n = 1$ and $p = 6$ or 8;

20 $m = 7$ and $n = 1$ and $p = 6$; or

$m = 10$ and $n = 1$ and $p = 3$

or a pharmaceutically acceptable salt thereof.

6. The method according to claim 4, wherein the compound administered is

25

a) 2-[[[(Z)-1-oxo-9-octadecenyl]amino]-4-thiazoleacetic acid;

b) 2-[[[(E)-1-oxo-9-octadecenyl]amino]-4-thiazoleacetic acid;

c) 2-[(1-oxo-9-octadecynyl)amino]-4-thiazoleacetic acid;

d) 2-[[[(Z)-1-oxo-6-octadecenyl]amino]-4-thiazoleacetic acid;

e) 2-[[[(Z)-1-oxo-9-hexadecenyl]amino]-4-thiazoleacetic acid;

30

f) 2-[[[(E)-1-oxo-9-hexadecenyl]amino]-4-thiazoleacetic acid;

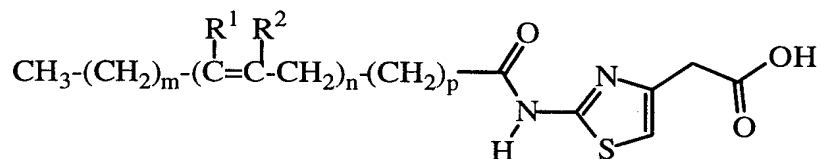
g) 2-[[[(E)-1-oxo-11-octadecenyl]amino]-4-thiazoleacetic acid; or

h) 2-[[[(Z,Z,Z)-1-oxo-9,12,15-octadecatrienyl]amino]-4-thiazoleacetic acid

or a pharmaceutically acceptable salt thereof.

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7. A method of modulating glucose levels in a mammal in need thereof which comprises administering to said mammal, a compound of formula I having the structure



I

wherein

R^1, R^2 are both hydrogen or form a bond, or are each, independently, alkyl of 1-6 carbon atoms or aryl of 6-12 carbon atoms;

$m = 0 - 10$;

$n = 1-3$; and

10 $p = 0 - 10$;

with the proviso that $m + p$ is less than or equal to 15;

or a pharmaceutically acceptable salt thereof.

8. The method according to claim 7, wherein

15 $m = 1$ and $n = 3$ and $p = 6$;

$m = 4$ and $n = 3$ and $p = 3$;

$m = 5$ and $n = 1$ and $p = 6$ or 8;

$m = 7$ and $n = 1$ and $p = 6$; or

$m = 10$ and $n = 1$ and $p = 3$

20 or a pharmaceutically acceptable salt thereof.

9. The method according to claim 8, wherein the compound administered is

a) 2-[(Z)-1-oxo-9-octadecenyl]amino]-4-thiazoleacetic acid;

b) 2-[(E)-1-oxo-9-octadecenyl]amino]-4-thiazoleacetic acid;

25 c) 2-[(1-oxo-9-octadecynyl)amino]-4-thiazoleacetic acid;

d) 2-[(Z)-1-oxo-6-octadecenyl]amino]-4-thiazoleacetic acid;

e) 2-[(Z)-1-oxo-9-hexadecenyl]amino]-4-thiazoleacetic acid;

f) 2-[(E)-1-oxo-9-hexadecenyl]amino]-4-thiazoleacetic acid;

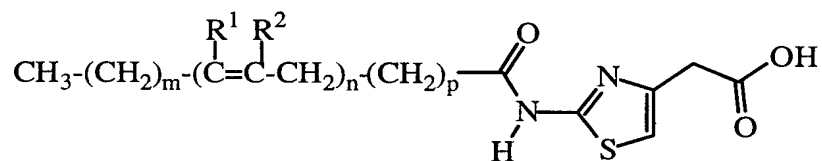
g) 2-[(E)-1-oxo-11-octadecenyl]amino]-4-thiazoleacetic acid; or

30 h) 2-[(Z,Z,Z)-1-oxo-9,12,15-octadecatrienyl]amino]-4-thiazoleacetic acid

or a pharmaceutically acceptable salt thereof.

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10. A method of treating primary hypertension in a mammal in need thereof, which comprises administering to said mammal a compound of formula I having the structure



I

5 wherein

R^1 , R^2 are both hydrogen or form a bond, or are each, independently, alkyl of 1-6 carbon atoms or aryl of 6-12 carbon atoms;

$m = 0 - 10$;

$n = 1-3$; and

10 $p = 0 - 10$;

with the proviso that $m + p$ is less than or equal to 15;

or a pharmaceutically acceptable salt thereof.

11. The method according to claim 10, wherein

15 $m = 1$ and $n = 3$ and $p = 6$;

$m = 4$ and $n = 3$ and $p = 3$;

$m = 5$ and $n = 1$ and $p = 6$ or 8;

$m = 7$ and $n = 1$ and $p = 6$; or

$m = 10$ and $n = 1$ and $p = 3$

20 or a pharmaceutically acceptable salt thereof.

12. The method according to claim 10, wherein the compound administered is

a) 2-[(Z)-1-oxo-9-octadecenyl]amino]-4-thiazoleacetic acid;

b) 2-[(E)-1-oxo-9-octadecenyl]amino]-4-thiazoleacetic acid;

25 c) 2-[(1-oxo-9-octadecynyl)amino]-4-thiazoleacetic acid;

d) 2-[(Z)-1-oxo-6-octadecenyl]amino]-4-thiazoleacetic acid;

e) 2-[(Z)-1-oxo-9-hexadecenyl]amino]-4-thiazoleacetic acid;

f) 2-[(E)-1-oxo-9-hexadecenyl]amino]-4-thiazoleacetic acid;

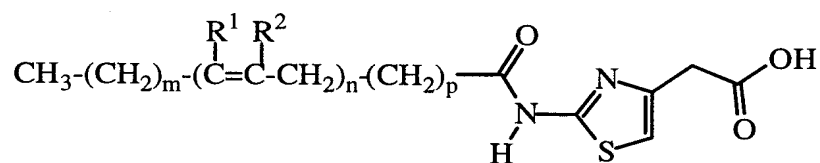
g) 2-[(E)-1-oxo-11-octadecenyl]amino]-4-thiazoleacetic acid; or

30 h) 2-[(Z,Z,Z)-1-oxo-9,12,15-octadecatrienyl]amino]-4-thiazoleacetic acid

or a pharmaceutically acceptable salt thereof.

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13. A method of treating atherosclerosis in a mammal in need thereof, which comprises administering to said mammal a compound of formula I having the structure



I

5 wherein

R^1 , R^2 are both hydrogen or form a bond, or are each, independently, alkyl of 1-6 carbon atoms or aryl of 6-12 carbon atoms;

$m = 0 - 10$;

$n = 1-3$; and

10 $p = 0 - 10$;

with the proviso that $m + p$ is less than or equal to 15;

or a pharmaceutically acceptable salt thereof.

14. The method according to claim 13, wherein

15 $m = 1$ and $n = 3$ and $p = 6$;

$m = 4$ and $n = 3$ and $p = 3$;

$m = 5$ and $n = 1$ and $p = 6$ or 8;

$m = 7$ and $n = 1$ and $p = 6$; or

$m = 10$ and $n = 1$ and $p = 3$

20 or a pharmaceutically acceptable salt thereof.

15. The method according to claim 13, wherein the compound administered is

a) 2-[(*(Z)*-1-oxo-9-octadecenyl)amino]-4-thiazoleacetic acid;

b) 2-[(*(E)*-1-oxo-9-octadecenyl)amino]-4-thiazoleacetic acid;

25 c) 2-[(1-oxo-9-octadecynyl)amino]-4-thiazoleacetic acid;

d) 2-[(*(Z)*-1-oxo-6-octadecenyl)amino]-4-thiazoleacetic acid;

e) 2-[(*(Z)*-1-oxo-9-hexadecenyl)amino]-4-thiazoleacetic acid;

f) 2-[(*(E)*-1-oxo-9-hexadecenyl)amino]-4-thiazoleacetic acid;

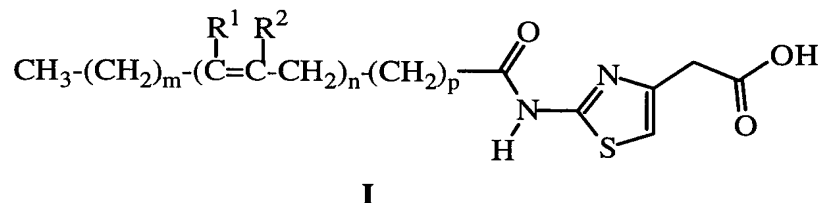
g) 2-[(*(E)*-1-oxo-11-octadecenyl)amino]-4-thiazoleacetic acid; or

30 h) 2-[(*(Z,Z,Z)*-1-oxo-9,12,15-octadecatrienyl)amino]-4-thiazoleacetic acid

or a pharmaceutically acceptable salt thereof.

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16. A compound of formula I having the structure



wherein

- 5 R^1, R^2 are both hydrogen or form a bond, or are each, independently, alkyl of 1-6 carbon atoms or aryl of 6-12 carbon atoms;
 $m = 0 - 10$;
 $n = 1-3$; and
 $p = 0 - 10$;
 10 with the proviso that $m + p$ is less than or equal to 15;
 or a pharmaceutically acceptable salt thereof.
17. The method according to claim 16, wherein
 $m = 1$ and $n = 3$ and $p = 6$;
 15 $m = 4$ and $n = 3$ and $p = 3$;
 $m = 5$ and $n = 1$ and $p = 6$ or 8;
 $m = 7$ and $n = 1$ and $p = 6$; or
 $m = 10$ and $n = 1$ and $p = 3$
 or a pharmaceutically acceptable salt thereof.
- 20 18. The compound according to claim 16, which is
 a) 2-[(Z)-1-oxo-9-octadecenyl]amino]-4-thiazoleacetic acid;
 b) 2-[(E)-1-oxo-9-octadecenyl]amino]-4-thiazoleacetic acid;
 c) 2-[(1-oxo-9-octadecynyl)amino]-4-thiazoleacetic acid;
 25 d) 2-[(Z)-1-oxo-6-octadecenyl]amino]-4-thiazoleacetic acid;
 e) 2-[(Z)-1-oxo-9-hexadecenyl]amino]-4-thiazoleacetic acid;
 f) 2-[(E)-1-oxo-9-hexadecenyl]amino]-4-thiazoleacetic acid;
 g) 2-[(E)-1-oxo-11-octadecenyl]amino]-4-thiazoleacetic acid; or
 h) 2-[(Z,Z,Z)-1-oxo-9,12,15-octadecatrienyl]amino]-4-thiazoleacetic acid
 30 or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

International Application No

PC 1/US 99/10212

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D277/46 A61K31/425

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98 04536 A (OTSUKA PHARMACEUTICAL COMPANY, LIMITED) 5 February 1998 (1998-02-05)	1, 16
A	page 410 -page 413, line 11	1
A	page 424; claim 33	
A	EP 0 790 057 A (HISAMTSU PHARMACEUTICAL CO. INC.) 20 August 1997 (1997-08-20) page 2 -page 3, line 24 & WO 96 16650 A cited in the application	1, 16
A	US 5 688 821 A (KENNETH LEWIS KEES) 18 November 1997 (1997-11-18) cited in the application the whole document	1, 16



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

7 October 1999

Date of mailing of the international search report

13/10/1999

Name and mailing address of the ISA

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Authorized officer

Kyriakakou, G

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 99/10212

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 1-15, 17
are directed to a method of treatment of the human/animal
body, the search has been carried out and based on the alleged
effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 99/10212

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9804536 A	05-02-1998	AU 695817 B	20-08-1998
		AU 3635497 A	20-02-1998
		CA 2233611 A	05-02-1998
		CN 1198160 A	04-11-1998
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EP 790057 A	20-08-1997	AU 689972 B	09-04-1998
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		US 5856347 A	05-01-1999
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		WO 9616650 A	06-06-1996
US 5688821 A	18-11-1997	NONE	